Safety and Histological Effect of Liquid Nitrogen Metered Spray Cryotherapy in the Lung

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To the Editor:

Chronic bronchitis is characterized by inflammation, cough, and increased mucus production. There is no cure, and current treatment options are limited to addressing symptoms (1). The RejuvenAir System (CSA Medical, Inc., Lexington, MA) is a device designed to bronchoscopically address chronic bronchitis by delivering liquid nitrogen (LN_2) as a metered cryospray (MCS). MCS is controlled by a thermocouple on the delivery catheter that feeds back real-time information regarding the amount of LN_2 being delivered. That amount is tailored such that each bronchial airway receives a standardized amount of LN_2 based on airway size, leading to a 10-mm circular cryoablation with a depth between 0.1 and 0.5 mm.

On the basis of older generations of LN_2 spray interventions (2, 3), it is hypothesized that LN_2 can induce an airway tissue healing effect by destroying the hyperplastic goblet cells and excess submucous glands. The extracellular matrix facilitates rapid regrowth of normal epithelium without scarring, a hallmark of cryoablation (4, 5). The healing resulting from LN_2 MCS is the basis of this proposed treatment.

To start this project, we evaluated the safety of delivering LN_2 in two small pilot studies. Two sprays were delivered into the lobar and first segmental bronchi, which would be the most distal extent of the anticipated airway treatment in chronic bronchitis, based on the significant goblet cell pathology present in these areas (6). The primary endpoint for each study was the evaluation of device-related serious adverse events (SAEs). The initial study (NCT02106143, previously reported as an American Thoracic Society 2016 conference abstract [7]) was conducted in subjects who were scheduled to undergo lobectomy or pneumonectomy immediately after MCS. The second study (NCT02483052) evaluated the same device-related SAEs as the initial study, plus postprocedure safety, as these subjects had a planned lobectomy after MCS. Both studies had evaluation of potential histologic effects of MCS as a secondary endpoint, and the specimens were reviewed by an independent pathologist skilled in cryothermic tissue injuries (J.C.). Procedures were performed by flexible bronchoscopy under general anesthesia, using an endotracheal tube with positive pressure ventilation. During the LN_2 spray, the endotracheal tube was disconnected from the ventilator with the cuff deflated, both to allow N_2 gas egress. Major inclusion criteria included FEV_1 $\geqslant$50% of predicted, no bullae $>$3 cm, and no previous lung surgery of any sort. Both studies were approved by the local ethics committees, and all patients provided informed consent.

Overall, 16 subjects were enrolled and treated at three sites in Europe and Canada. The initial study enrolled 11 (three women/eight men) subjects, with a mean ($\pm$SD) age of 65.8 $\pm$ 8.9 years (range, 45.7–74.8 years), a mean FEV_1% predicted of 86.1 $\pm$ 28.1% (range, 46–132%), and a smoking history of 28.3 $\pm$ 20.5 pack-years (range, 0.02–54.0 pack-years). Mean time to the scheduled surgical resection after MCS was 37.7 $\pm$ 21.8 minutes (range, 15–80 minutes). In the delayed study, five subjects (four women/one man) were enrolled, with a mean age of 66.8 $\pm$ 6.2 years (range, 59.2–74.0 years), a mean FEV_1% predicted of 72.8 $\pm$ 16.5% (range, 51–91%), and a smoking history of 29.8 $\pm$ 22.4 pack-years (range, 4.5–47.0 pack-years). Mean time to resection after MCS was 14 $\pm$ 1.4 days (range, 12–16 days). Final histopathological diagnosis was non–small-cell lung cancer in 15 patients, and small-cell lung cancer in 1 patient.

All intended 32 LN_2 MCS were given. The delivery of MCS was both feasible and safe, with no device-related (S)AEs. There were no intraoperative complications with stable vital signs, and no technical difficulties preventing application of MCS. Three SAEs were reported in each study, all determined to be unrelated to the study device, the MCS treatment, or bronchoscopy, as adjudicated by an independent medical monitor. The SAEs all occurred after completion of MCS and video-assisted thoracoscopic surgery (VATS): atrial fibrillation (8 days after), mucus plug (3 days after), and death more than 30 days after LN_2 spray resulting from hospital-acquired pneumonia after pneumonectomy in the nontreated lung; one subject had intraoperative bleeding during VATS (14 days after MCS), an immediate postoperative bleeding, and bleeding again 18 days after VATS.

Eight immediate resection subjects' treated bronchial segments were available, with five of them revealing the presence of the intended cryothermic histologic changes. In the regions with greater epithelial changes, minimal to mild acute inflammation was present. In two specimens, there was extension into the submucosa, with cryothermic changes involving the submucosal glands with preservation of the underlying submucosal structure, including no effect on the underlying cartilage (Figure 1).

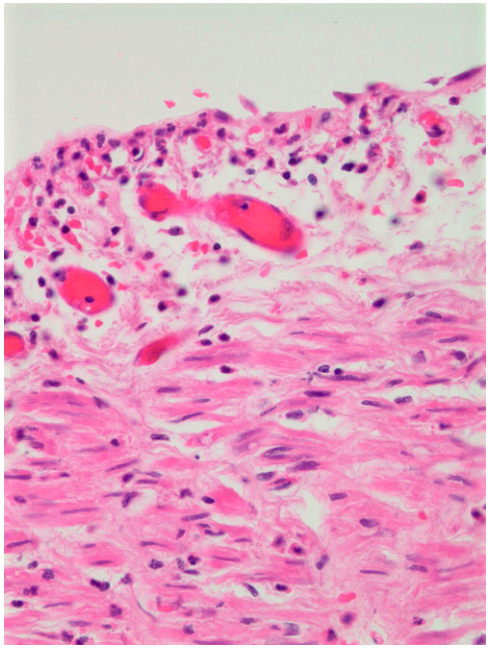

Figure 1. Representative 2-hour post–liquid nitrogen metered cryospray–treated bronchial micrograph demonstrating surface and superficial ductal epithelial removal to a depth up to 500 μ (hematoxylin and eosin stained, 400$\times$ magnification). The submucosal extracellular matrix remains intact (nondenatured) with mild capillary congestion and minimal luminal-oriented acute inflammation and edema.

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In the delayed resection study, a bronchoscopy was performed just before lung resection took place. The video of these bronchoscopies was independently reviewed by an experienced bronchoscopist (R.B.), with three subjects showing a slight mucosal whitening, one of which seemed to represent subtle white rings consistent with cryoablation. Airway caliber was normal, and there were no signs of infection. All five subjects had bronchial segments submitted for histopathological evaluation. Because of the lack of visual mucosal changes after fixation, identification of the treatment sites represented a major limitation in the subsequent histologic evaluation. Histology findings were consistent with complete re-epithelialization at the treatment site. No persistent treatment-related epithelial erosions, acute inflammation, granulomatous inflammation, mucosal necrosis, fibroproliferative healing, or collagenous luminal narrowing were identified (*see* Figure 2 for a representative example). The bronchial cartilage rings primarily appeared unremarkable, with one specimen showing focal cartilage ring necrosis, consistent with possible cryothermic injury or nonspecific degenerative changes.

In summary, the data obtained in both clinical trials met the primary and secondary endpoints, with safe delivery of MCS to the segmental and/or lobar bronchi without device-related SAEs. Histology from immediate resection specimens documented MCS effect and nonscarring healed tissue from the delayed resection group.

The information learned from this study is important for the future development of a bronchoscopic treatment for patients who suffer from chronic bronchitis. Although this future intended indication was not specifically studied in these patients, they share some chronic bronchitis characteristics, such as exposure to cigarettes and most having chronic obstructive pulmonary disease. Using MCS in a similar population and determining the immediate and delayed healing response has provided important information in the stepwise clinical development of the system. These results warrant further investigation in a larger clinical trial targeting patients with chronic bronchitis, which is currently underway (NCT02483637). ■

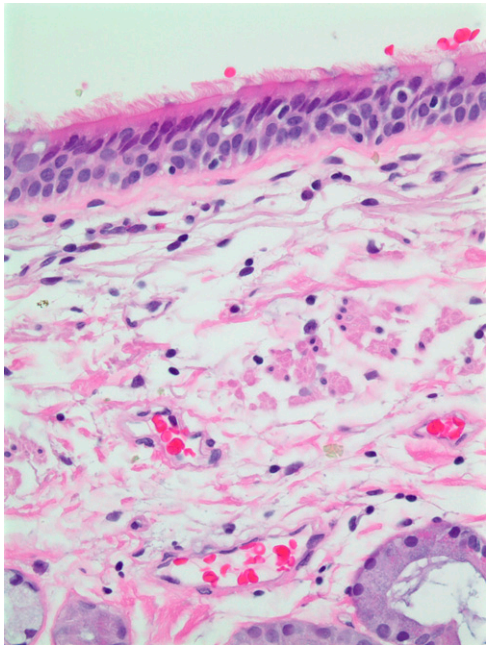

Figure 2. Representative 14-day post–liquid nitrogen metered cryospray–treated bronchial micrograph demonstrating complete rejuvenative healing, characterized by pseudostratified respiratory epithelium with occasional goblet cells, preservation of the submucosa and cartilage, and absence of inflammation and fibrosis (hematoxylin and eosin stained, 400× magnification).

Author disclosures are available with the text of this letter at www.atsjournals.org.

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